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10/719,540	11/20/2003	Ron L. Hale	00063.01R	3439

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IP Department
Alexza Molecular Delivery Corporation
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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,540	HALE ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 24* is/are rejected.

7)☒ Claim(s) *1,11,17 and 18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/24/05;9/24/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-24 are pending. Claims 1-20 and 24 are under consideration in the instant office action.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-20 and 24, drawn to a method of treating pain comprising the administration of a compound selected from the group consisting of loxapine, pharmaceutically acceptable salts of loxapine, and loxapine prodrugs, classified in class 514, subclass 185.

II. Claims 21-23, drawn to a composition comprising (a) an analgesic selected from a group consisting of loxapine, pharmaceutically acceptable drugs thereof, and loxapine prodrugs and (b) a pharmaceutically acceptable carrier, classified in class 424, subclasses 43-45, depending upon the carrier selected.

The inventions are distinct, each from the other because of the following reasons:

Inventions II and I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the composition as claimed can be used in the treatment of schizophrenia and other psychological disorders.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

I n the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

During a telephone conversation with Ms. Kathy Lobel Rice, Esq. on May 19, 2006 at approximately 4pm EST a provisional election was made without traverse to prosecute the invention of Group I, claims 1-20 and 24. Affirmation of this election must be made by applicant in replying to this Office action. Claims 21-23 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f). Applicant is respectfully encouraged to see § 608.01 of the MPEP, regarding the incorporation by reference of material in a U.S. patent or patent application, which itself incorporates essential material by reference:

> "In any application, which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) **a U.S. patent or application which itself incorporates "essential material" by reference**, or (4) a foreign application." See MPEP § 608.01 (p).

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claims 1, 11, 17, and 18 are objected to because of the following informalities: a comma should be inserted in claim 1, line 3 after the word "loxapine;" it is respectfully suggested that the word "of" be inserted in claim 11, line 4 between "mg" and "loxapine;" the word "an" should be inserted in claim 17, line 2 between the words "via" and "delivery;" the indefinite article, "a," should be inserted in claim 18, line 2 between the words "as" and "thin." Appropriate correction is required.

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3 and 10-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Dehaven et al. (WO 02/060870; IDS).

Applicant recites a method of treating pain in a subject comprising administering to said subject an effective amount of a compound selected from loxapine, pharmaceutically acceptable salts of loxapine, and prodrugs thereof. Claim 10 recites an administration dosage from about

0.3 to about 20 mg and claims 11-15 recite properties resulting from the administration of said loxapine dosage.

Dehaven discloses in claims 1 and 3 **methods of inducing analgesia in a patient** comprising administration of compounds of **formula (I) and (Ib)**, both of which encompass **loxapine**. Single dosages of these compounds for **injection**, infusion, or ingestion will generally vary from **5 to about 1,500 mg**, with a preferred dosage ranging from **7.5 to about 45 mg** per day, administered orally, with appropriate adjustment for body weight of an individual (pg. 17, lines 4-13). The properties recited in claims 11-15 are characteristic of injection administration of loxapine, as evidenced by Applicant's admission on page 13, paragraph [0041] of the instant specification. Injection administration encompasses intravenous administration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.

3. Ascertaining the differences between the prior art and the claims at issue; and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns et al. (U.S. Patent No. 5,284,133).

Applicant Claims

Applicant recites a method of treating pain in a subject comprising administering to said subject an effective amount of a compound selected from loxapine, pharmaceutically acceptable salts of loxapine, and prodrugs thereof. Claim 10 recites an administration dosage from about 0.3 to about 20 mg and claims 11-15 recite properties resulting from the administration of said loxapine dosage.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Burns teaches an inhalation device provided with a mechanism to assure patient compliance with a drug dosage regimen (abstract) and that patient non-compliance with

inhalation devices has been recognized as a major medical problem (col. 2, lines 39-40). Burns teaches an inhalation device as well as an actuator/timing controller that operates in conjunction with an inhalation device to prevent both patient under compliance with prescribed dosing and patient abuse or dependence on prescribed medication (col. 1, lines 19-24). Burns also teaches that many drugs, which are traditionally delivered by intravenous, subcutaneous, intramuscular, or intraperitoneal injection, can advantageously be delivered by **aerosol inhalation**. Delivery of a drug to the alveoli in the lung to a point where the drug can pass through the lung mucosa can be accomplished with **an MDI, nebulizer, dry powder inhaler, or like device which operates by a patient inspiring solubilized or micronized drug deep into the lung**. In order for the drug to penetrate deeply in the lung, the particles containing the drug should be on the order of a few microns (0.2 to 20) in size. Aerosol delivery is particularly advantageous because first-pass metabolism of the drug by the liver and kidneys is avoided. In addition, the objectionable requirement of finding a suitable injection site and piercing the skin with a needle is avoided. Furthermore, a wide variety of systemically active drugs would benefit from aerosol delivery via inhalation, including neuroleptics, psychotropic drugs, and narcotic antagonists, analgesics, etc (col. 5, lines 29-57). In addition, as delivering systemic drugs by aerosol administration gains wider acceptance, there will be increased demands on the safety of inhalation devices. It is expected that with some drugs, relying on proper patient aerosol administration will not be acceptable. For example, with **headache analgesics**, including, **loxapine hydrochloride**, there may be a tendency of some patients to overdose themselves (col. 7, lines 3-5, 10-17, and 27-30). Burns states that his invention is specifically directed to providing inhalation devices, such as MDIs, nebulizers, and dry powder inhalers, with a safety alarm and actuator mechanism which

both aids in assuring that a patient administers in a timely manner a required dose of drug and prevents overdosing a prescribed drug (col. 7, lines 40-45).

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

The teachings of Burns focus upon his invented inhalation devices; designed to aid with proper aerosol inhalation administration, correct dosage delivery, and the prevention of overdosing of a prescribed drug.

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been apparent to a person of ordinary skill in the art at the time of the instant invention that one could utilize Burn's inhalation device to deliver loxapine hydrochloride in the practice of a method of treating pain, because loxapine hydrochloride is a known headache analgesic. A skilled artisan would have been motivated to deliver loxapine hydrochloride to treat headache pain (including migraine pain), because this use of loxapine hydrochloride (LoxHCl) is taught by Burns. A skilled artisan would have been further motivated to select LoxHCl because it is expected that there may be a tendency of some patients to overdose themselves with CNS-affecting drugs, including LoxHCl; and because Burn's device is designed to administer drugs via the inhalation administration of aerosols while assuring proper dosing and preventing overdosing. Regarding the distinction between different types of headache pain (i.e. see claims 4-7), it would have been obvious to a skilled artisan that LoxHCl

would be useful in the treatment of these different kinds of headaches/migraines, because it is a known headache analgesic. It is art recognized that analgesics relieve pain.

Claims 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns et al. (U.S. Patent No. 5,284,133) as applied to claims 1-9 and 24 above, and further in view of Drug Information Handbook, 2nd edition (Lexi-Comp, Inc.: Cleveland, 1994-1995, pp 554-555) ("DIH").

Applicant Claims

Applicant recites a method of treating pain comprising administering to a subject in need of treatment an effective amount of loxapine, loxapine prodrugs, or pharmaceutically acceptable salts thereof, wherein the dosage of loxapine is from about 0.3 to about 20 mg, and administration has the property of resulting in maximal loxapine serum concentration within 15 (claim 13) or 30 (claim 12) minutes of delivery so as to result in a peak rate of increase in blood levels of at least about 1 ng/ml/minute (claim 14) and/or a loxapine blood level of at least about 5 ng/ml within about 15 minutes of administration (claim 15).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Burns have been set forth above. The DIH teaches different oral dosages of loxapine for adults of 10 mg twice daily or more as needed to control psychotic symptoms; that the usual dose range is 60-100 mg/day divided in doses taken 2-4 times/day (i.e. single dosages ranging from 15-25 mg); and that dosages greater than 250 mg/day are not

recommended. For I.M. administration the recommended dosages are 12.5-50 mg every 4-6 hours or longer as needed and change to oral therapy as soon as possible (pg 555 of DIH).

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Burns lacks the teaching of loxapine dosages. This deficiency is cured by the teachings of the DIH.

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant application to combine the teachings of Burns and the DIH, because the DIH is a well-known reference for commercially available therapeutic agents. Regarding the dosages taught by the DIH, it would have been apparent to a skilled artisan that the dosages required for inhalation administration would be lower than those for oral administration, because via inhalation administration the disadvantage of first-pass metabolism of the drug by the liver and kidneys is avoided (Burns). Therefore, less drug would be needed if administered by inhalation. The skilled artisan would utilize the teachings of the DIH regarding the oral doses as a maximum starting point from which to undertake routine optimization of dosage amounts as practiced in the art. A person of ordinary skill in the art would have had a reasonable expectation of success upon combination of the prior art references, because Burns teaches the inhalation administration of LoxHCl as a headache analgesic and the DIH provides the skilled artisan with guidance as to adverse reactions, overdose/toxicology, dosage recommendations, drug interactions,

pharmacodynamics of loxapine needed to effectively and safely administer said drug. Regarding the properties associated with inhalation administration, such as systemic delivery of drug and rapid attainment of maximal loxapine serum concentrations in specific periods of time, it would have been apparent to a skilled artisan at the time of the instant invention that these properties are characteristic of inhalation administration, as the Applicant admits on page 13, paragraph [0041], of the instant specification.

Claims 16-17 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns et al. (U.S. Patent No. 5,284,133) as applied to claims 1-9 and 24 above, and further in view of Nguyen et al. (U.S. Patent No. 7,040,314).

Applicant Claims

Applicant recites a method of treating pain comprising administering to a subject in need of treatment an effective amount of loxapine, loxapine prodrugs, or pharmaceutically acceptable salts thereof, wherein loxapine or pharmaceutically acceptable salt/prodrug thereof is administered via inhalation using a rapid-heating delivery article or a thin-film drug delivery article (claim 16), wherein said compound is vaporized and condensed to provide at least 50% recovery of said compound in an aerosol containing less than about 5% w/w degradation products.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Burns have been set forth above. Nguyen teaches an aerosol generating device that generates an aerosol by passing liquid aerosol formulation through a flow passage heated to convert the liquid into a vapor, which is mixed with air to form an aerosol, wherein said device can be incorporated in a hand held inhaler. In some embodiments, particles of the aerosol consist essentially of the second component. The aerosol can be delivered to a targeted portion of the lung using the inhaler (abstract). The liquid aerosol formulations include at least one high volatility carrier, preferably a liquid solvent, and a second component, which is a solute dissolved in the liquid carrier, including any suitable medicament that may be delivered to a patient by an aerosol. Suitable medicaments include **analgesics and anxiolytics (e.g. loxapine)** (col. 3, lines 49-52; col. 4, lines 58-67; col. 5, line 26, and claims 18-20). Nguyen teaches that the aerosol-generating device preferably generates aerosols in which 95% of the aerosol particles (aerosol droplets) have a **size between 0.5 microns to about 2.5 microns**, and that the aerosol may contain particles with sizes less than 0.1 microns (col. 15, lines 20-25). In Example 1 and Figure 7, Nguyen teaches that the aerosols generated from a 1% albuterol ethanolic solution by the invented device had an **average MMAD of 0.66 microns**. Nguyen's claims 18, 20, 26, and 28 recite a method of generating an aerosol, wherein the second component is a **medicament**, **the aerosol is a condensation aerosol** and that the aerosol particles having a **MMAD of less than 2.5 microns, respectively**. In Example 7, Nguyen stated that the test results depicted in Fig. 11 demonstrated that the aerosol generating device can be used to prepare budesonide aerosols with **up to 100% recoveries, no observable degradation**, and sufficiently small particle sizes for inhalation, using a carrier, including ethanol.

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Burns lacks the teaching of a rapid-heating drug delivery article. This deficiency is cured by the teachings of Nguyen.

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Burns and Nguyen, because Burns teaches an inhalation device as well as an actuator/timing controller that operates in conjunction with an inhalation device to prevent both patient under compliance with prescribed dosing and patient abuse or dependence on prescribed medication. The inhalation devices specifically suited for use in combination with Burns teachings include metered-dose inhalers, nebulizers, and dry powder inhalers. Both MDIs and nebulizers are art recognized to deliver aerosols generated from liquid formulations and Nguyen teaches an aerosol generating device wherein formulations comprising a liquid carrier and a medicament are heated to generate aerosols suitable for inhalation administration and characterized by high recovery percentages and very low amounts of degradation products. Therefore, it would have been apparent to a skilled artisan at the time of the instant invention that one could combine the teachings of Burns, suitably used with both MDIs and nebulizers, and have a reasonable expectation of successfully delivering drugs, including loxapine, as aerosols having desirable aerodynamic properties (low MMAD, high recovery, low amount of degradation products) and in such a manner as to improve patient dosage compliance and prevent patient overdose.

Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns et al. (U.S. Patent No. 5,284,133) as applied to claims 1-9 and 24 above, and further in view of Rabinowitz et al. (US 2004/0009128).

Applicant Claims

Applicant recites a method of treating pain comprising administering to a subject in need of treatment an effective amount of a loxapine compound, loxapine prodrugs, or pharmaceutically acceptable salts thereof, wherein loxapine or pharmaceutically acceptable salt/prodrug thereof is administered via inhalation using a thin-film drug delivery article (claim 16), wherein said compound is vaporized and condensed to provide at least 50% recovery of said compound in an aerosol containing less than about 5% w/w degradation products (17), and said loxapine compound is coated on a substrate as a thin film having a film thickness between 0.5 and 20 microns (claim 18).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Burns have been set forth above. Rabinowitz discloses a method of delivering an amine drug in an aerosol form is comprising: a) **heating a coating (i.e. a film), which includes an amine drug salt on a substrate contained in a device to a temperature sufficient to volatilize the amine drug** from the coating, b) by said heating, forming an amine drug vapor, and c) during said heating, drawing air through said device, **condensing said vapor to form aerosol particles containing less than 10% degradation products of the compound** (abstract). Rabinowitz also teaches that in more preferred embodiments, the coating of the amine

drug salt used has a **thickness between about 0.5 and 20 microns**, and the aerosol particles generated have **a mass median aerodynamic diameter between about 1 and 5 micrometers** [0025]. **Loxapine** is an amine drug, and is identified by Rabinowitz in [0063] as an example of a suitable drug for use in his invention from which an amine salt may be formed. The drug amine salts selected for vaporization preferably have the following characteristics: a molecular weight greater than 200 g/mole and a decomposition index less than 0.15. Typical examples of such preferred drug amine salts that are anxiolytics include **loxapine** [0100]. In Examples 3-4, Rabinowitz teaches general methods of screening drug amines (Example 3) and drug amine salts (Example 4) for aerosolization preferability. In Example 5, Rabinowitz teaches that aerosols formed by his method have an MMAD ranging from 1-3 microns.

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Burns lacks the teaching of a thin-film drug delivery article. This deficiency is cured by the teachings of Rabinowitz.

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Burns and Rabinowitz, because Burns teaches an inhalation device as well as an actuator/timing controller that operates in conjunction with an inhalation device to prevent both patient under compliance with prescribed dosing and patient abuse or dependence on prescribed medication. A skilled artisan would have been motivated to

combine the teachings of Burns and Rabinowitz, because it is expected that with some drugs, relying on proper patient aerosol administration will not be acceptable, such as, **headache analgesics**, including, **loxapine hydrochloride**, which may also suffer from a tendency in some patients to overdose themselves (Burns, col. 7, lines 3-5, 10-17, and 27-30). It would have been apparent to a skilled artisan at the time of the instant invention that one could combine the teachings of Burns, suitable for use with inhalation devices, and have a reasonable expectation of successfully delivering drugs, including loxapine, as aerosols having desirable aerodynamic properties (low MMAD and a low amount of degradation products) and in such a manner as to improve patient dosage compliance and prevent patient overdose. Rabinowitz' device is an inhalation device, therefore, a person of ordinary skill in the art would have had a reasonable expectation of success upon combination of the prior art references.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 16-17, and 19 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7, 9, 10, 12, and 13 of U.S. Patent No. 6,716,416 (USPN '416). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are overlapping in scope and mutually obvious. The claims of USPN '416 encompass the steps of generating the condensation aerosol obviously encompassed by the steps incorporated in the administration of loxapine as described in claims 16-20 of the instant application, wherein loxapine is volatilized using a thin film drug delivery article by heating a film to generate condensation particles comprising less than 5% degradation particles (e.g. at least about 97% loxapine).

Claims 1 and 16-20 (claim 20, only with copending '877) provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12, 15, 16, and 18 of copending Application No. 10/653,876 (copending '876) and claims 1 and 7-9 of copending Application No. 10/633,877 (copending '877). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are overlapping in scope and mutually obvious. The claims of copending '876 encompass the steps of generating the condensation aerosol obviously encompassed by the steps incorporated in the administration of loxapine as described in claims 16-20 of the instant application, wherein loxapine is volatilized by heating a thin film having a thickness ranging from between 0.05 to 20 microns and comprising a loxapine film on a substrate contained within a drug delivery article

that generates condensation aerosol particles comprising less than 5% degradation particles Similarly, the cited claims of copending '877 are drawn to an article for use in an aerosol device comprising a drug composition film (i.e. loxapine) having a film thickness between 0.05-20 microns, which upon heating generates a condensation aerosol comprising less than 5% degradation products. Therefore, the examiner concludes that claims 12, 15, 16, and 18 of copending Application No. 10/653,876 (copending '876) and claims 1 and 7-9 of copending Application No. 10/633,877 (copending '877) *prima facie* obvious over claims 1 and 16-20 (claim 20, only with copending '877) of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 1, 11, 17, and 18 are objected. Claims 1-20 and 24 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0664. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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